Drug-Induced Neutropenia

A Focus on Rituximab-Induced Late-Onset Neutropenia

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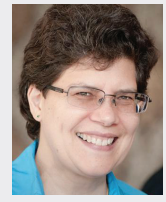
Welcome to the Pharmacovigilance Forum, where we report on interesting adverse drug reactions (ADRs), including drug-induced disease.



All pharmaceuticals carry a risk of ADRs, whether they are new and improved, generic agents, older brand products, complex biologics, or biosimilars. Each Pharmacovigilance Forum will discuss noteworthy topics related to ADRs in the clinical realm. Every medication has the potential to cause disease, but clinicians are often slow to recognize drug therapy as an etiological factor. I encourage anyone with a potentially interesting case to contact me, to publish ADRs here or elsewhere, and to report ADRs to the Food and Drug Administration's MedWatch program.

—Michele B. Kaufman

INTRODUCTION

Drug-induced neutropenia is a potentially serious and life-threatening adverse event that may occur secondary to therapy with a variety of agents. Cytotoxic chemotherapy can cause a predictable and dose-related decrease in neutrophil count. Neutropenia secondary to other medications tends to be an idiosyncratic reaction either as an immune-mediated reaction or because of direct myeloid cell line damage. This effect has been associated with a variety of medications including, but not limited to, clozapine, dapsone, methimazole, penicillin, rituximab, and procainamide.[1] For a comprehensive list of medications associated with the development of neutropenia, see Table 1. Neutropenia from nonchemotherapy drugs is much less common than neutropenia secondary to chemotherapy.[2]

Rituximab is an anti-CD20 monoclonal antibody indicated for the treatment of a variety of B-cell lymphocytic malignancies, including chronic lymphocytic leukemia (CLL), follicular lymphoma, and diffuse large B-cell lymphoma.[3] Rituximab is also used for the management of several autoimmune disorders, such as rheumatoid arthritis and Wegener's granulomatosis. In the treatment of B-cell malignancies, this monoclonal antibody exerts its anticancer activity by depleting malignant B cells via mechanisms such as complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and by inducing apoptosis.[4] In the treatment of cancer, rituximab can be administered as monotherapy or in combination with chemotherapy agents, depending on the indication.

Common adverse events associated with rituximab therapy include acute infusion reactions, lymphopenia, infection, and asthenia.[3] Delayed and late-onset serious side effects may include progressive multifocal leukoencephalopathy, reactivation of hepatitis B, and interstitial pneumonitis. When rituximab was added onto chemotherapy regimens, it was found to be safe and tolerable without adding significant hematological toxicities. Postmarketing studies and case reports have shown that rituximab has the potential to cause delayed and late-onset neutropenia that may vary in severity.[5–7] We report the cases of two patients who were treated for hematological malignancies with rituximab that led to severe, late-onset neutropenia resulting in neutropenic fever, which required hospitalization.

PATHOPHYSIOLOGY

Neutropenia is defined as having an absolute neutrophil count (ANC) of less than 500 cells/mm^3 and is a common adverse event associated with many cytotoxic chemotherapy agents.[8] During cytotoxic chemotherapy, neutropenia typically occurs during the nadir—the lowest value to which the neutrophil count will fall following drug administration. The nadir typically occurs 10 to 14 days following chemotherapy administration during each treatment cycle. Neutrophil recovery will usually occur in three to four weeks following treatment. Exceptions to this include agents such as mitomycin, carmustine, and lomustine, which have a delayed nadir of about four to six weeks following administration of each cycle. During treatment with these agents, neutrophil recovery will usually occur six to eight weeks following treatment. The nadir and neutropenia associated with most types of cytotoxic chemotherapy are considered to be rather predictable in onset and occurrence.

In patients receiving cancer treatment regimens containing rituximab with cytotoxic chemotherapy (e.g., anthracyclines, purine antagonists, alkylating agents, etc.), the nadir of the patient's neutrophil count is expected to occur 10 to 14 days following administration of each cycle of treatment. Rituximab has been reported to cause neutropenia, but with a delayed

Table 1 Medications Associated With The Development of Neutropenia[1,2]

Nonchemotherapy	
• Clozapine	• Procainamide
• Dapsone	• Propylthiouracil
• Hydroxychloroquine	• Quinidine/Quinine
• Infliximab	• Rituximab
• Lamotrigine	• Sulfasalazine
• Methimazole	• Trimethoprim-sulfamethoxazole
• Oxacillin	
• Penicillin G	• Vancomycin
Chemotherapy	
• Alkylating agents	• Hydroxyurea
• Anthracyclines	• Mitomycin C
• Antimetabolites	• Taxanes
• Camptothecins	• Vinblastine
• Epipodophyllotoxins	

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and often unpredictable onset. Rituximab-associated late-onset neutropenia has been defined in the literature as neutropenia developing at least three to four weeks following the end of rituximab administration despite a complete recovery of ANC following chemotherapy.[9] It has also been reported that rituximab may induce neutropenia more than 40 days after the end of treatment.[10] Neutropenia with cytotoxic chemotherapy recovers with a very predictable pattern and is typically short-lived in duration; however, rituximab-induced late-onset neutropenia may be prolonged and result in a very unpredictable recovery time. Without the utilization of granulocyte-colony stimulating factors (GCSFs), rituximab-induced late-onset neutropenia may last a median of six to 77 days.[11]

Most cases of rituximab-induced late-onset grade 1–3 neutropenia are self-limiting and resolve without any complications. However, there is the possibility of more severe cases in grade 4 neutropenia.[10,12] In grade 3 or 4 neutropenia, there is a potential for prolonged and serious life-threatening infectious complications. The delayed onset, unpredictable occurrence, and neutrophil recovery associated with rituximab-induced late-onset neutropenia can create a clinical challenge for practitioners. Diligent patient follow-up is needed to monitor for this adverse event, and therapeutic intervention may be necessary in severe cases that may result in neutropenic fever.

MECHANISM OF ADVERSE DRUG REACTION

Most cytotoxic chemotherapy exerts its pharmacological activity by causing DNA damage in either a cell-specific or cell-nonspecific manner. By damaging the DNA of malignant cells, chemotherapy is able to produce killer malignant cells. Many chemotherapy agents cause bone marrow suppression resulting in neutropenia, which leads to an increased risk of infection. The mechanism by which rituximab may induce neutropenia has yet to be fully elucidated; however, a variety of theories exist.

After rituximab administration, antibodies against neutrophils may be produced, resulting in neutropenia.[13] It may also develop due to aberrant B-cell reconstitution after rituximab administration. Another theory is that homeostasis of granulocytes may be disturbed by chemokine stromal-derived factor-1 interacting with B-lymphocyte recovery. One of the most compelling theories is that it may occur due to polymorphisms in the immunoglobulin G (IgG) Fc receptor (FcγR). Patients harboring the FcγRIIIa 158 V/F polymorphism were found to have a higher incidence of rituximab-induced neutropenia.[14] The presence of this polymorphism may facilitate neutropenia following rituximab administration by mediating antibody-dependent cell-mediated cytotoxicity on malignant and nonmalignant B cells, thus increasing the degree of B-cell depletion.

INCIDENCE AND RISK FACTORS

The reported incidence of rituximab-induced late-onset neutropenia varies within the literature. This adverse drug reaction (ADR) may occur in 8% to 27% of cancer patients treated with rituximab.[15] The incidence of rituximab-induced late-onset neutropenia has been reported to be much lower in patients being managed with rituximab for autoimmune disease. These rates are as low as 1.3% to 2.3%.[16] Despite the proposed high incidence of this ADR, many of the episodes are self-limiting and without any apparent clinical significance. In rare cases, severe neutropenia has the potential to occur, which can place patients at risk for life-threatening infectious complications. Severe neutropenia resulting in neutropenic fever and infection can lead to hospitalization, the need for broad-spectrum antibiotics, and the potential sequelae of bacteremia, and it can be fatal.

Multiple studies have evaluated the risk factors for developing rituximab-induced late-onset neutropenia. Patients with advanced stages of malignancy and those more than 60 years of age are at greater risk.[6,9] Previous treatment with purine analogs or methotrexate and prior autologous peripheral blood stem cell transplantation may also be risk factors for developing rituximab-induced late-onset neutropenia. In addition, patients harboring the IgG FcγRIIIa 158 V/F polymorphism are at high risk for developing this ADR.[12,14] In patients receiving rituximab for noncancer indications, age and female gender have been found to increase the risk for this adverse event.[16]

MANAGEMENT

Infectious complications, such as neutropenic fever, that may occur because of severe and prolonged neutropenia secondary to rituximab treatment should be managed with antimicrobial therapy. Antimicrobials should be selected and modified based on guideline recommendations.[8] Empiric treatment of neutropenic fever usually includes an antipseudomonal beta-lactam, such as cefepime, ceftazidime, piperacillin-tazobactam, meropenem, or imipenem. Treatment against methicillin-resistant *Staphylococcus aureus* (MRSA) with agents such as vancomycin should be included in empiric antimicrobial regimens when other additional clinical indicators are present, such as pneumonia, skin or soft tissue infection, or suspected catheter-related infection, or if the patient is hemodynamically unstable.

GCSFs can also be used in patients with neutropenic fever with additional risk factors for severe complications, such as those with an ANC of less than 100 cells/mm^3 and/or with pneumonia, hypotension, multi-organ failure, or invasive fungal infections.[17] GCSFs, such as Neupogen (filgrastim, Amgen), Granix (tbo-filgrastim, Cephalon, Inc.), and Zarxio (filgrastim-sndz, Sandoz), stimulate and promote the maturation and activation of neutrophils. This class of drugs can also enhance the exodus of mature neutrophils trapped within the bone marrow. Through these mechanisms, GCSFs have demonstrated proven efficacy in their ability to reduce the incidence, magnitude, and duration of neutropenia following chemotherapy administration.

In severe cases of rituximab-induced late-onset neutropenia, especially with infectious complications, the utilization of filgrastim or a filgrastim biosimilar may be warranted. Filgrastim products are especially useful in managing patients treated with rituximab because they address the unpredictable nature of neutrophil recovery and possible prolonged neutropenic duration. No specific recommendations regarding the optimal ANC target, frequency, and duration of administration of filgrastim products have been proposed to manage this adverse event. The drug is typically administered once daily until neutrophil recovery when it is utilized for neutropenia prophylaxis in patients with nonmyeloid malignancies receiving

myelosuppressive chemotherapy.[18] Although rituximab-induced late-onset neutropenia has the potential to be a long-lasting complication, neutrophil recovery with the use of a filgrastim product can occur in as few as four days.[9] To keep a patient's ANC greater than 1,000 cells/mm^3, maintenance strategies using the drug once or twice weekly may be employed for several months for patients with prolonged neutropenia despite initial neutrophil recovery.[5]

Two recent cases are described below.

Case 1

A 70-year-old man with a history of stage IVA small lymphocytic lymphoma (SLL) presented to the emergency department (ED) with complaints of fatigue and fever. Forty-two days prior to presentation, his SLL was treated with bendamustine 189 mg (90 mg/m^2) on days 1 and 2 and rituximab 788 mg (375 mg/m^2) on day 1 of a 28-day cycle. Subsequently, his treatment was temporarily held due to severe thrombocytopenia secondary to bendamustine; he was scheduled to resume treatment with a reduced dose of bendamustine within two days of presentation to the ED. His past medical history was also significant for peripheral vascular disease, coronary artery disease, hypertension, and chronic kidney disease. His home medication list included aspirin 81 mg daily, atorvastatin 40 mg daily, carvedilol 3.125 mg twice daily, clopidogrel 75 mg daily, hydrochlorothiazide 12.5 mg daily, losartan 25 mg daily, and a multivitamin.

Pertinent laboratory data on his initial presentation can be seen in Table 2. His ANC was 360 cells/mcL (neutropenic). The patient had not demonstrated neutropenia from the time of his diagnosis until his ED presentation. On presentation, the patient had a maximum body temperature (T_{max}) of 103.2° F, a blood pressure of 125/48 mm Hg, and a heart rate of 114 beats per minute. He was admitted for empirical treatment and management of neutropenic fever and was initiated on cefepime 2 g intravenously (IV) every eight hours and tbo-filgrastim 480 mcg subcutaneously once daily. Blood cultures showed *Pseudomonas aeruginosa* that was sensitive to ciprofloxacin, cefepime, piperacillin-tazobactam, and meropenem. Cefepime was continued for the duration of his four-day hospitalization, and he was discharged on oral ciprofloxacin to complete his antibiotic course. Filgrastim was continued for a total of three doses. On hospital day 2, neutrophil recovery was evident with his ANC rising to 1,800 cells/mcL. Upon further follow-up, no active antineoplastic regimens were subsequently utilized, and laboratory tests revealed no further episodes of neutropenia.

Table 2 Patient Laboratory Values

Tests and Vital Signs (normal range)	Hospitalization Day			
	Day 1	Day 2	Day 3	Day 4
Case 1				
WBC x 10^3 cells/mm^3 (3.5–11 x 10^3 cells/mm^3)	0.8	2.6	4.6	7.1
ANC, cells/mm^3 (> 1,500 cells/mm^3)	360	1,768	N/A	5,183
Hemoglobin, g/dL (13.3–17.7 g/dL)	10	8	7.7	7.7
Hematocrit, % (40%–52%)	26.2	27.4	22.1	21.6
Platelets x 10^9/L (150–400 x 10^9/L)	117	90	95	106
Blood pressure, mm Hg (90–149/60–90 mm Hg)	125/48	138/76	145/60	116/52
Pulse, bpm (60–120 bpm)	114	92	78	72
T_{max}, °F (97.8–99)	103.2	101.8	100	99.4
Case 2				
WBC x 10^3 cells/mm^3 (3.5–11 x 10^3 cells/mm^3)	0.8	1.7	2.3	3.7
ANC, cells/mm^3 (> 1,500 cells/mm^3)	208	578	989	5,698
Hemoglobin, g/dL (13.3–17.7 g/dL)	10.1	9.4	9.5	8.9
Hematocrit, % (40%–52%)	28.7	25.9	26.8	24.7
Platelets x 10^9/L (150–400 x 109/L)	132	74	92	108
Blood pressure, mm Hg (90–149/60–90 mm Hg)	106/71	137/67	131/74	122/62
Pulse, bpm (60–120 bpm)	101	88	84	87
T_{max}, °F (97.8–99.5)	103	98.4	98.3	97.8

ANC = absolute neutrophil count; bpm = beats per minute; T_{max} = maximum body temperature; WBC = white blood cell count.

Case 2

A 71-year-old woman with a long history of CLL presented to the ED with complaints of fever and right foot pain. Her CLL had been under observation for 17 years, but five months prior to presentation, she began treatment for CLL secondary to new-onset autoimmune hemolytic anemia and thrombocytopenia. She received four cycles of bendamustine 157 mg (90 mg/m^2) on days 1 and 2 and rituximab 653 mg (375 mg/m^2) on day 1 every 28 days. When she was evaluated for a fifth chemotherapy cycle about a month before her ED presentation, neutropenia

was identified, and her treatment was discontinued. Her past medical history was also significant for hypertension, type-2 diabetes mellitus, and gastroesophageal reflux disease. Her home medications included lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, and pantoprazole 40 mg daily.

Pertinent laboratory data for Case 2 can be found in Table 2. Her ANC was 208 cells/mcL (neutropenic). On presentation, the patient had a T_{max} of 103° F, a blood pressure of 106/71 mm Hg, and a heart rate of 101 beats per minute. She was admitted for empirical treatment and management of neutropenic fever. Cefepime 2 g IV piggyback (IVPB) every eight hours was initiated, along with vancomycin 1.5 g IVPB every 12 hours. She also received filgrastim 480 mcg subcutaneously once daily. Vancomycin was empirically started because of a suspected skin and soft-tissue infection on her right foot. Blood cultures were negative. Podiatry was consulted for the foot ulcer, for which an incision and drainage were performed. Cultures of the ulcer grew *Pasteurella canis*, and antibiotics were de-escalated to oral ciprofloxacin 500 mg twice daily for 10 days. Tbo-filgrastim 480 mcg was administered subcutaneously daily for a total of three days. Neutrophil recovery to an ANC of 1,750 cells/mcL occurred on the final day of administration. The patient was discharged after a four-day hospitalization. Follow-up laboratory tests did not reveal any further episodes of neutropenia.

CONCLUSION

Rituximab can cause a delayed and late-onset neutropenia that may last for an unpredictable amount of time. Although most cases appear to be self-limiting and resolve without issue, rituximab-induced late-onset neutropenia may result in serious life-threatening complications requiring immediate medical intervention. When patients with autoimmune disease or cancer are treated with rituximab, it is important to be aware of rituximab-induced neutropenia, which can occur long after therapy cessation. This adverse event can pose a challenge for clinicians and requires close patient follow-up during rituximab administration as well as after therapy has ended. Compared with what is reported in the literature, our two patients presented in a very similar fashion, given the delayed onset of the neutropenia and the swift ANC recovery following the administration of a filgrastim product.

Given the unclear nature and mechanism of rituximab-induced late-onset neutropenia, it is not fully known and understood if re-treatment with rituximab is a viable and safe option for patients. It has been previously reported that rechallenging a patient with rituximab following an episode of severe late-onset neutropenia can lead to recurrent episodes.[19] With the possibility of recurrence and the unclear risks and implications of re-treatment, the decision to administer further doses of rituximab should be made on a case-by-case basis. Future research is needed in this area.

REPORTING ADVERSE DRUG REACTIONS

All ADRs should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The Food and Drug Administration (FDA) 3500 Voluntary Adverse Event Report Form can be accessed easily online for reporting ADRs at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm.

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes. The FDA is also interested in any unlabeled ADRs for new drugs (e.g., usually those approved within the previous two years).

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